PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference 09716	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/000627	13.01.2005	14.01.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant
TAKEDA PHARMACEUTICAL COMPANY LIMITED

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP Facsimile No.	Authorized officer Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claim 10 relates to a method for treatment of the human body.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-4, 8, 9, 11	YES
	Claims	1, 5-7	NO
Inventive step (IS)	Claims		YES
	Claims	1-9, 11	NO
Industrial applicability (IA)	Claims	1-9, 11	YES
	Claims		NO

2. Citations and explanations:

Document 1: WO, 2004-002957, A1 (Actelion Pharmaceuticals, Ltd.), 8 January, 2004 (08.01.04)
Document 2: WO, 03-101964, A1 (Takeda Chemical Industries, Ltd.), 11 December, 2003 (11.12.03)
Document 3: JP, 8-67678, A (Takeda Chemical Industries, Ltd.), 12 March, 1996 (12.03.96)
Document 4: JP, 7-10844, A (Takeda Chemical Industries, Ltd.), 13 January, 1995 (13.01.95)
December 5: WO, 02-081457, A1 (Glaxo Group Ltd.), 17 October, 2002 (17.10.02)
December 6: WO, 01-025219, A1 (Glaxo Group Ltd.), 12 April, 2001 (12.04.01)

(1) The subject matters of claims 1 and 5-7 do not appear to be novel or to involve an inventive step in view of document 1 cited in the ISR.

Document 1 describes a compound corresponding to the general formula (I) described in claim 1.

Document 1 further describes that the compound is used for treatment of pulmonary hypertension, circulatory organ diseases, kidney diseases, immunosuppression after transplant, glaucoma etc.

Document 1 does not disclose a tachykinin receptor antagonism. However, the invention of the application concerned, a tachykinin receptor antagonist, is also used for treatment of pulmonary hypertension, circulatory organ diseases, kidney diseases, immunosuppression after transplant, glaucoma etc. So, the scope of application and medical use of document 1 cannot be distinguished from that of the invention of the application concerned.

Therefore, the subject matters of claims 1 and 5-7 are considered to be the same as the invention described in document 1 cited in the ISR.

(2) The subject matters of claims 2-4 do not appear to involve an inventive step in view of document 1 cited in the ISR and documents 2-6 cited in the ISR.

See (1) above-mentioned.

The compound relating to claims 2-4 differs from the compound described in document 1 in the substituent which bonds with a nitrogen-containing heterocycle (corresponding to an A ring) and benzene rings (corresponding to a B ring and a C ring) in the general formula (I) described in claim 1.

Documents 2-6 describe various compounds that have a structure similar to that of the compound described in document 1 and are useful as medicines. However, they also describe that acyl is preferable as a substituent bonding with nitrogen of a nitrogen-containing heterocycle and alkyl halide is preferable as a substituent on a benzene ring.

Accordingly, a person skilled in the art could have easily conceived of applying the substituent described in documents 2-6 to the compound useful as a medicine described in document 1.

Therefore, the compound relating to claims 2-4 is not recognized to have an unexpected effect in comparison with the publicly known compounds described in the above documents.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

(3) The subject matters of claims 8, 9 and 11 do not appear to involve an inventive step in view of document 1 cited in the ISR and documents 2-6 cited in the ISR.

See (1) and (2) above-mentioned.

As described in documents 2-6, various compounds are known which are useful as a tachykinin receptor antagonist that comprises a compound to which a nitrogen-containing heterocycle and two benzene rings are indispensable. The compound relating to claims 1-4 differs from the compound described in document 2 only in that methylene bonds to the nitrogen-containing heterocycle (corresponding to an A ring) and the benzene ring (corresponding to a B ring) in the general formula (I) described in claim 1 by an amide bond.

However, documents 3-6 describe various compounds that are useful as a tachykinin receptor antagonist which bonds, by an amide bond, with methylene bonding to the nitrogen-containing heterocycle and the benzene ring.

Accordingly, a person skilled in the art could have easily conceived of employing an amide bond in the bonding portion of methylene bonding with the nitrogen-containing heterocycle and the benzene ring in the tachykinin receptor antagonist described in document 2.

Therefore, the tachykinin receptor antagonist relating to claims 8, 9 and 11 is not recognized to have an unexpected effect in comparison with the tachykinin receptor antagonist described in the above documents.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. VI **Certain documents cited**

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/year)	Filing date (day/*month*/year)	Priority date (valid claim) (*day*/month/*year*)
WO 2004/105738 A2 (ACTELION PHARMACEUTICALS, LTD.) **[EX]**	09.12.2004	12.05.2004	**30.05.2003**

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/year)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

There are expressions "may have a substitutent" in claims 1-3 and "prodrug" in claims 5, 6 and 11. What structure the compound included into the invention has is made ambiguous by these expressions. Even allowing for the descriptions in the specification, it is not recognized that a structure of the compound is clearly defined.

Therefore, claims 1-3, 5, 6, 11 and the specification do not meet the prescribed requirements so sufficiently that an international investigation can be meaningfully performed.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

IPC

Int. CL^{7} A61P1/18, 3/00, 5/00, 7/00, 9/00, 11/00, 11/02, 13/02

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Applicant
TAKEDA PHARMACEUTICAL COMPANY LIMITED

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☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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Name and mailing address of the ISA/JP Facsimile No.	Authorized officer Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

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c. time of filing/furnishing

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4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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☐ the entire international application

☒ claims Nos. 10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claim 10 relates to a method for treatment of the human body.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

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the computer readable form
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-4, 8, 9, 11	YES
	Claims	1, 5-7	NO
Inventive step (IS)	Claims		YES
	Claims	1-9, 11	NO
Industrial applicability (IA)	Claims	1-9, 11	YES
	Claims		NO

2. Citations and explanations:

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Therefore, the subject matters of claims 1 and 5-7 are considered to be the same as the invention described in document 1 cited in the ISR.

(2) The subject matters of claims 2-4 do not appear to involve an inventive step in view of document 1 cited in the ISR and documents 2-6 cited in the ISR.

See (1) above-mentioned.

The compound relating to claims 2-4 differs from the compound described in document 1 in the substituent which bonds with a nitrogen-containing heterocycle (corresponding to an A ring) and benzene rings (corresponding to a B ring and a C ring) in the general formula (I) described in claim 1.

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Accordingly, a person skilled in the art could have easily conceived of applying the substituent described in documents 2-6 to the compound useful as a medicine described in document 1.

Therefore, the compound relating to claims 2-4 is not recognized to have an unexpected effect in comparison with the publicly known compounds described in the above documents.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

(3) The subject matters of claims 8, 9 and 11 do not appear to involve an inventive step in view of document 1 cited in the ISR and documents 2-6 cited in the ISR.

See (1) and (2) above-mentioned.

As described in documents 2-6, various compounds are known which are useful as a tachykinin receptor antagonist that comprises a compound to which a nitrogen-containing heterocycle and two benzene rings are indispensable. The compound relating to claims 1-4 differs from the compound described in document 2 only in that methylene bonds to the nitrogen-containing heterocycle (corresponding to an A ring) and the benzene ring (corresponding to a B ring) in the general formula (I) described in claim 1 by an amide bond.

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Accordingly, a person skilled in the art could have easily conceived of employing an amide bond in the bonding portion of methylene bonding with the nitrogen-containing heterocycle and the benzene ring in the tachykinin receptor antagonist described in document 2.

Therefore, the tachykinin receptor antagonist relating to claims 8, 9 and 11 is not recognized to have an unexpected effect in comparison with the tachykinin receptor antagonist described in the above documents.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/year)	Filing date (day/*month*/year)	Priority date (valid claim) (*day*/month/*year*)
WO 2004/105738 A2 (ACTELION PHARMACEUTICALS, LTD.) **[EX]**	09.12.2004	12.05.2004	**30.05.2003**

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/year)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000627

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

There are expressions "may have a substitutent" in claims 1-3 and "prodrug" in claims 5, 6 and 11. What structure the compound included into the invention has is made ambiguous by these expressions. Even allowing for the descriptions in the specification, it is not recognized that a structure of the compound is clearly defined.

Therefore, claims 1-3, 5, 6, 11 and the specification do not meet the prescribed requirements so sufficiently that an international investigation can be meaningfully performed.

WRITTEN OPINION OF THE
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International application No.
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

IPC

Int. CL^{7} A61P1/18, 3/00, 5/00, 7/00, 9/00, 11/00, 11/02, 13/02